Anticancer Agents Pathway Example

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Agents Pathway — Cancer Stem Cell, Gene Expression, & Epigenetic Targets

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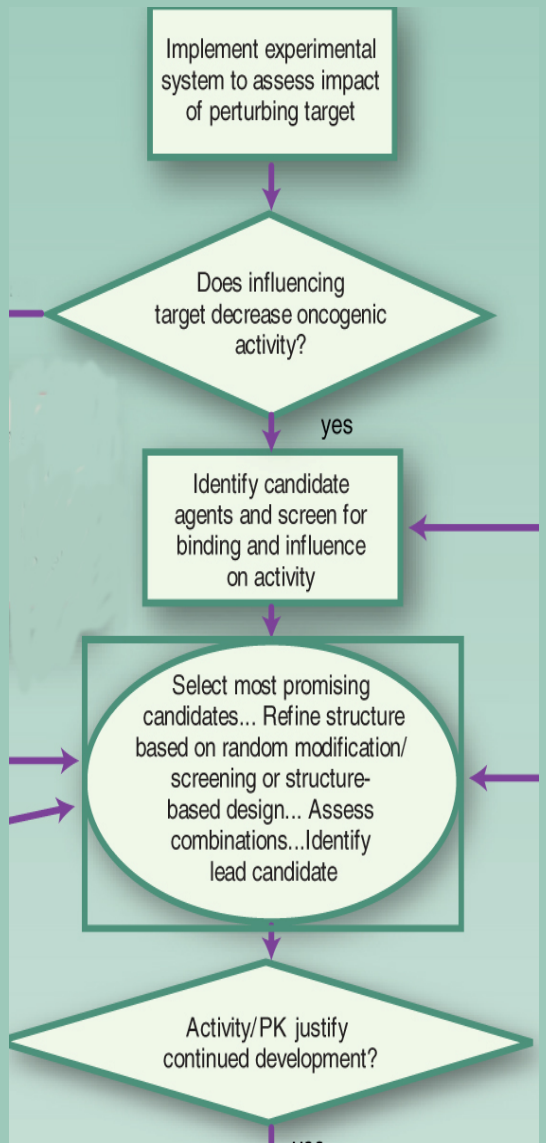
Targeting Self-Renewing Cells (SNC) in Cancer

Detailed characterization of stem-cell regulatory networks active in cancer is likely to yield powerful diagnostic and prognostic markers and, quite possibly, *attractive targets for therapeutic intervention*.

Pathways in developmental biology a key?

Ben-Porath et al, Nat Genet, 40:499, 2008

Agent Pathway:
Creation of Modality

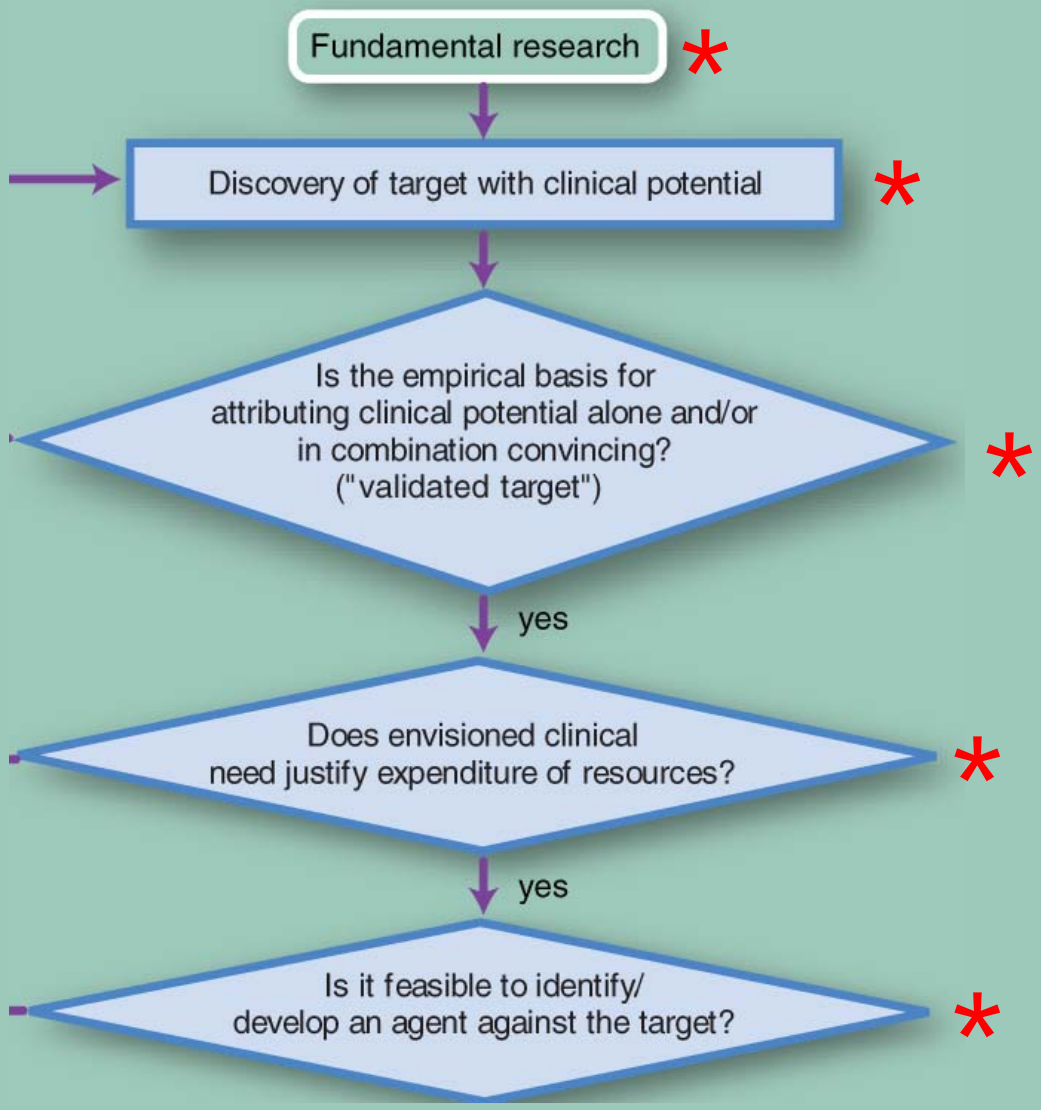


- **Where are we in developing the candidate drugs/targeting molecules, etc?**
  - **SHH-Gli**
  - **Wnt**

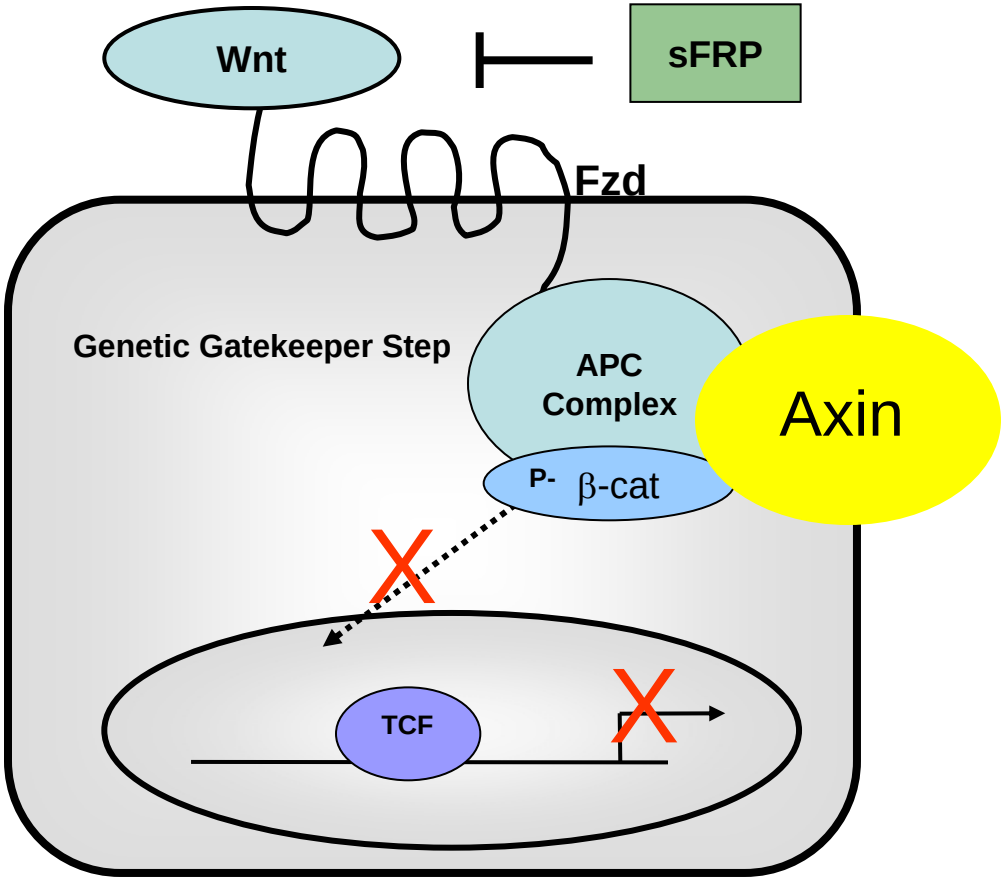
RJ Coffey and colleagues - Vanderbilt

  - **Epigenetic approaches**

Initial Steps Taken



Agent Pathway:



NORMAL

Differentiation Homeostasis

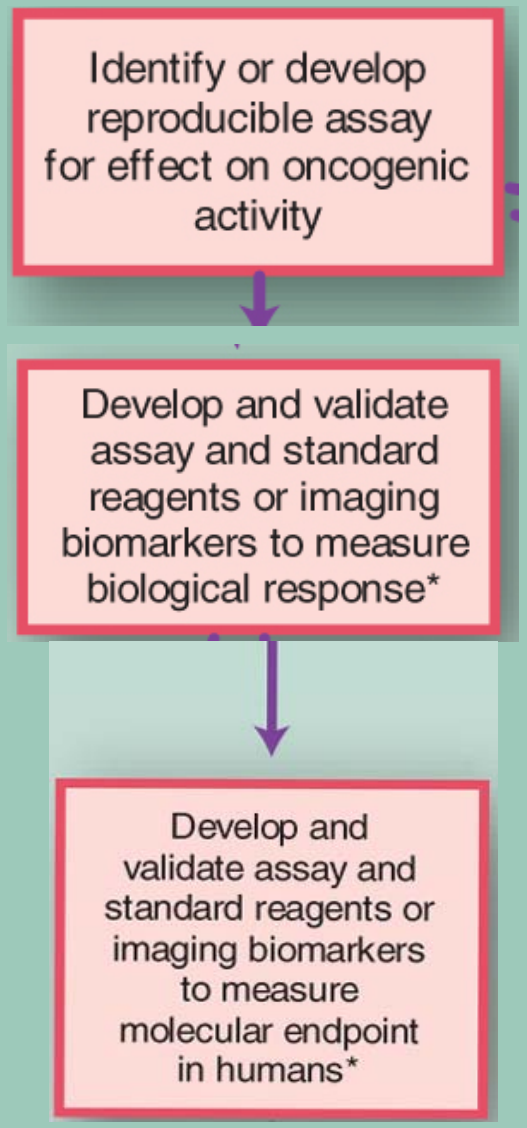
The Screen

- Hypothesized that Wnt mediated axin degradation is critical for pathway activation and a small molecule which blocks axin degradation would potently drive down β-catenin concentrations and prevent signaling.

- Developed a high-throughput assay that recapitulates activation of the canonical Wnt pathway in Xenopus egg extracts. Measured activated pathway in Xenopus extracts to screen drug libraries for regulators of β-catenin and axin turnover.

- Identified 19 lead compounds → VU-WS30 (FDA approved for another use.

Assays and Endpoints



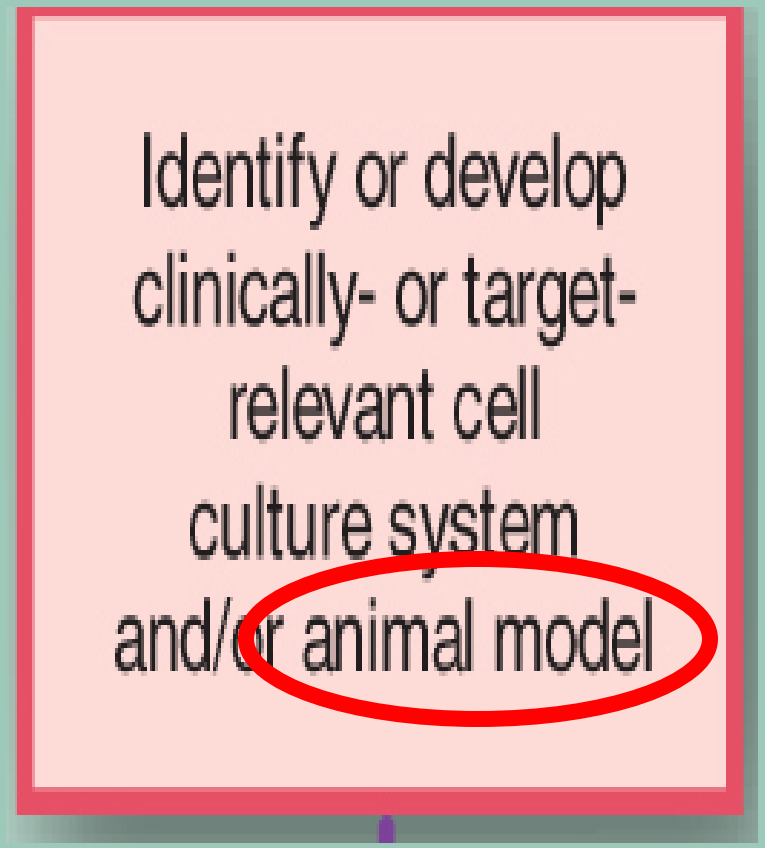
Assays and Endpoints

- **Blocks induction of secondary axis formation in Xenopus embryos in a concentration-dependent manner (an indication of Wnt pathway inhibition in vivo).**

- **Can alter vulval and cuticle formation in C. elegans and D. melanogaster, respectively, demonstrating that the molecular target of VU-WS30 is conserved among metazoans.**

- **Inhibits axin degradation in Xenopus extracts and in cell culture, suggesting that VU-WS30 downregulates the canonical Wnt pathway by potentiating the function of axin.**

Cell and Animal Model Readouts



- **In cultured mammalian HEK293 cells, VU-WS30 inhibits Wnt3a-induced expression from a TOPFLASH reporter (EC50 ~55 nM), as well as the endogenous Wnt gene targets, Myc, Dkk1 and Axin2**
- **Inhibition of Wnt-mediated gene transcription by VU-WS30 correlates with decreased cytoplasmic β-catenin levels in these cells.**
- **In cancer cells, VU-WS30 inhibits β-catenin-driven proliferation of breast (MDA-MB231) and colon (SW480 and SW620) lines at similar concentrations (EC50 ~55 nM) yet is 100-fold less effective towards non-transformed, non-Wnt signaling human diploid fibroblast, suggesting specificity towards the β-catenin-mediated proliferation.**
- **Decreases cytoplasmic β-catenin levels and synergizes with 5-FU to induce apoptosis in these cancer cells. Actin staining reveals an alteration in cellular morphology suggestive of reversal of an epithelial-mesenchymal transition.**

What's Needed?

- **Drug developed as an anti-helminth agent — designed not to have systemic access — lead compound must be developed — chemistry**

- **PK, toxicity profiles, etc.**